

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|------------------|---|
| <p>(51) International Patent Classification ⁶ : A61K 31/695</p> | <p>A1</p> | <p>(11) International Publication Number: WO 95/15760 (43) International Publication Date: 15 June 1995 (15.06.95)</p> |
| <p>(21) International Application Number: PCT/US94/12702 (22) International Filing Date: 3 November 1994 (03.11.94) (30) Priority Data: 08/165,281 10 December 1993 (10.12.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/165,281 (CON) Filed on 10 December 1993 (10.12.93) (71) Applicant (for all designated States except US): MERRELL DOW PHARMACEUTICALS INC. [US/US]; 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, OH 45215-6300 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MAO, Simon, J., T. [US/US]; 9373 Kentonsrun Court, Loveland, OH 45140 (US). YATES, Mark, T. [US/US]; 126 Joliet Avenue, Cincinnati, OH 45215 (US). PARKER, Roger, A. [US/US]; 480 Meadowcrest Road, Cincinnati, OH 45231 (US).</p> | | <p>(74) Agent: PAYNE, T., Helen; Marion Merrell Dow Inc., 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, OH 45215-6300 (US). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report</i> <i>With amended claims.</i></p> |
| <p>(54) Title: METHOD OF LOWERING SERUM CHOLESTEROL LEVELS WITH 2,6-DI-ALKYL-4-SILYL-PHENOLS (57) Abstract <p>A method of lowering plasma cholesterol level in a patient with hypercholesterolemia, by administration of a compound of formula (I) wherein: R₁, R₂, R₃ and R₄ are each independently a C₁-C₆ alkyl group; Z is a thio, oxy or methylene group; A is a C₁-C₄ alkylene group; and R₅ is a C₁-C₆ alkyl or -(CH₂)_n-(Ar) wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or naphthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl.</p></p> <div data-bbox="779 1144 1364 1407"> <p style="text-align: right;">(I)</p> </div> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LK | Sri Lanka | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

-1-

5

METHOD OF LOWERING SERUM CHOLESTEROL LEVELS
WITH 2,6-DI-ALKYL-4-SILYL-PHENOLS

10

Coronary heart disease (CHD) remains the leading cause of death in the industrialized countries. Despite recent declines in CHD mortality, CHD is still responsible for more than 500,000 deaths in the U.S. annually. It is estimated
15 that CHD, directly and indirectly, costs the U.S. more than \$100 billion a year. The primary cause of CHD is atherosclerosis, a disease characterized by the deposition of lipids in the arterial vessel wall, resulting in a narrowing of the vessel passages and ultimately hardening the vascular
20 system.

Atherosclerosis as manifested in its major clinical complication, ischaemic heart disease, is thought to begin with local injury to the arterial endothelium followed by
25 proliferation of arterial smooth muscle cells from the medial layer to the intimal layer along with deposition of lipid and accumulation of foam cells in the lesion. As the atherosclerotic plaque develops, it progressively occludes more and more blood vessel and can eventually lead to
30 ischaemia or infarction. Therefore, it is desirable to provide a method of inhibiting the progression of atherosclerosis in patients in need thereof.

Hypercholesterolemia is an important risk factor
35 associated with CHD. For example, in December 1984, a

-2-

National Institute of Health Consensus Development Conference Panel concluded that lowering plasma cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will definitely reduce the risk of heart attacks due to CHD. Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density: chylomicrons, very low-density lipoproteins (VLDL), low density lipoproteins (LDL) and high-density lipoproteins (HDL). Chylomicrons mainly participate in transporting dietary triglycerides and cholesterol from the intestine to adipose tissue and liver. VLDL deliver endogenously synthesized triglycerides from liver to adipose and other tissues. LDL transport cholesterol to peripheral tissues and regulate endogenous cholesterol levels in those tissues. HDL transports cholesterol from peripheral tissues to the liver. Arterial wall cholesterol is derived almost exclusively from LDL (Brown and Goldstein, *Ann. Rev. Biochem.* 52, 223 (1983); Miller, *Ann. Rev. Med.* 31, 97 (1980)). In patients with low levels of LDL, the development of atherosclerosis is rare. Accordingly, it is desirable to provide a method for reducing plasma cholesterol in patients with hypercholesterolemia or at risk of developing hypercholesterolemia.

Elevated cholesterol levels are also associated with a number of disease states, including restenosis, angina, cerebral arteriosclerosis, and xanthoma. It is desirable to provide a method for reducing plasma cholesterol in patients with, or at risk of developing, restenosis, angina, cerebral arteriosclerosis, xanthoma, and other disease states associated with elevated cholesterol levels.

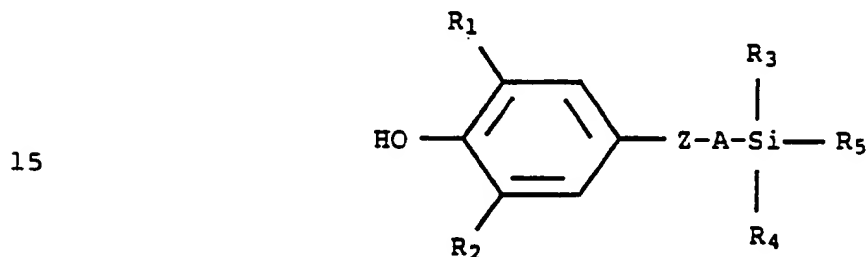
SUMMARY OF THE INVENTION

The present invention relates to the use of certain 2,6-di-alkyl-4-silyl-phenols to lower cholesterol levels in

-3-

patients with hypercholesterolemia. The present invention also relates to the use of certain 2,6-di-alkyl-4-silyl-phenols to lower cholesterol levels in patients with restenosis, angina, cerebral arteriosclerosis, xanthema and
 5 other disease states associated with elevated cholesterol levels.

The present invention relates to a method for lowering plasma cholesterol in a patient by administration of a
 10 compound of the formula of (1)



20 wherein:

R₁, R₂, R₃ and R₄ are each independently a C₁-C₆ alkyl group;
 Z is a thio, oxy or methylene group;
 A is a C₁-C₄ alkylene group; and
 25 R₅ is a C₁-C₆ alkyl or -(CH₂)_n-(Ar)
 wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or
 naphthyl unsubstituted or substituted with one to three
 substituents selected from the group consisting of
 30 hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C₁-C₆ alkyl" refers to a
 35 saturated hydrocarbyl radical of straight, branched or cyclic

-4-

configuration made up of from one to six carbon atoms. Included within the scope of this term are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tertiarybutyl, n-pentyl, n-hexyl, cyclohexyl and the like.

5

Likewise, the term "C₁-C₄ alkylene" refers to a saturated hydrocarbyldiyl radical of straight or branched configuration made up of from one to four carbon atoms. Included within the scope of this term are methylene, 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane-diyl, 1,2-propane-diyl, 1,3-butane-diyl, 1,4-butane-diyl and the like.

In those instances wherein R₅ is a -(CH₂)_n-(Ar) radical, the -(CH₂)_n- moiety represents a saturated hydrocarbyldiyl radical of straight chain configuration. The term "n" is defined as an integer 0, 1, 2 or 3. The moiety -(CH₂)_n- thus represents a bond, methylene, 1,2-ethanediyl or 1,3-propanediyl. The -(Ar) moiety represents an aryl radical defined as a substituted or unsubstituted phenyl or naphthyl group. In those instances wherein the -(Ar) moiety is a substituted aryl, the phenyl or naphthyl can bear from 1 to 3 substituents in any position otherwise occupied by a hydrogen atom. Substituents are selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro and C₁-C₆ alkyl group. Specifically included within the scope of the term -(CH₂)_n-(Ar) are phenyl; naphthyl; phenylmethyl; phenylethyl; 3,4,5-trihydroxyphenyl; 3,4,5-trimethoxyphenyl; 3,4,5-triethoxyphenyl; 4-chlorophenyl; 4-methylphenyl; 3,5-di-tertiarybutyl-4-hydroxyphenyl; 4-fluorophenyl; 4-chloro-1-naphthyl; 2-methyl-1-naphthylmethyl; 2-naphthylmethyl; 4-chlorophenylmethyl; 4-tertiarybutylphenyl; 4-tertiarybutylphenylmethyl and the like.

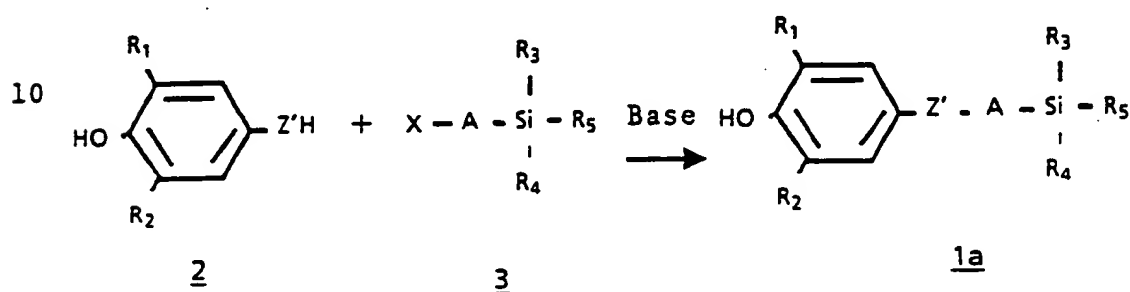
The compounds of formula (1) can be prepared by utilizing procedures and techniques well known and appreciated by one of

-5-

ordinary skill in the art. A general synthetic scheme for preparing compounds of formula (1) wherein Z is sulfur or oxygen is set forth in Scheme A, wherein all substituents, unless otherwise indicated, are previously defined.

5

Scheme A



$\text{Z}' = \text{S or O}$
 $\text{X} = \text{chlorine, bromine, or iodine}$

20 In general, a phenol of structure 1a can be prepared by reacting the appropriate 2,6-dialkyl-4-mercaptophenol or 2,6-dialkylhydroquinone of structure 2 (or suitably protected derivatives) with a non-nucleophilic base, such as sodium hydride or potassium carbonate, and the appropriate

25 haloalkylenesilane of structure 3, such as the appropriate chloroalkylenesilane, in a suitable aprotic solvent, such as dimethylformamide or dimethylacetamide, or in an aqueous solvent, such as water/2-butanone.

30 Starting materials for use in the general synthetic procedure outlined in Scheme A are readily available to one of ordinary skill in the art. For example, certain phenol starting materials for various compounds of formula (1) wherein Z is sulfur, such as 2,6-di-tertiarybutyl-4-

35

-6-

mercaptophenol, are described in U.S. Patent 3,576,883, U.S. Patent 3,952,064, U.S. Patent 3,479,407 and in Japanese Patent Application 73-28425. Also, silyl starting materials for various compounds of formula (1), such as (trimethylsilyl)-methyl iodide, (trimethylsilyl)methyl bromide, (trimethylsilyl)methyl chloride, (1-chloropropyl)trimethylsilane, are described in *Synthesis* 4, 318-19 (1988) and *J. Am. Chem. Soc.* 105, 5665-75 (1983).

10 In those instances where the 1-phenol functionality of a compound of structure 2 may react with the compounds of structure 3 under the conditions of the reaction, the 1-phenol functionality of compound of structure 2 may be blocked with standard phenol blocking agents which are well known and appreciated in the art. The selection and utilization of particular blocking groups are well known to one of ordinary skill in the art. In general, blocking groups should be selected which adequately protect the phenol in question during subsequent synthetic steps and which are readily removable under conditions which will not cause degradation of the desired product.

25 Examples of suitable phenol protecting groups are ethers, such as methoxymethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, t-butyl and benzyl; silyl ethers, such as trimethylsilyl and t-butyldimethylsilyl; esters, such as acetate and benzoate; carbonates, such as methylcarbonate and benzylcarbonate; as well as sulfonates, such as methanesulfonate and toluenesulfonate.

30

 In those instances where R₁ and R₂ are each t-butyl, the reaction of Scheme A may be conveniently carried out without blocking of the 1-phenol functionality.

35

-7-

The following examples present typical syntheses as described in Scheme A. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "mp" refers to melting point; "mg" refers to milligrams; "μM" refers to micromolar; "μg" refers to micrograms.

Example 1

2,6-Di-t-butyl-4[(dimethylphenylsilyl)methyl]thio-phenol

Mix 2,6-di-t-butyl-4-mercaptophenol (2.4g, 10mmol), potassium carbonate (1.4g, 10mmol), chloromethyldimethylphenylsilane (1.9g, 10mmol) and dimethylformamide (50mL) and stir overnight at room temperature under argon atmosphere. Dilute the mixture with ice-water and extract with ethyl ether. Wash the ethereal layer with water, then brine, filter through flourosil- Na_2SO_4 , and evaporate to an orange oil (3.5g). Purify the product by first distilling (bp 160-170°C @ 0.1 mm Hg), then subjecting to silica gel chromatography ($\text{CCl}_4:\text{CHCl}_3$ /1:1) to obtain the title compound as a light yellow oil which slowly crystallizes to a white waxy solid (2.3g, 59%).

Anal. Calcd for $\text{C}_{23}\text{H}_{34}\text{OSSi}$: C, 71.44; H, 8.86; S, 8.29;
Found: C, 71.14; H, 8.86; S, 7.98.

Example 2

2,6-Di-t-butyl-4[(dimethyldodecylsilyl)methyl]thio-phenol

Mix 2,6-di-t-butyl-4-mercaptophenol (2.4g, 10mmol), potassium carbonate (1.7g, 12.3mmol),

-8-

chloromethyldodecyldimethylsilane (2.8g, 10mmole) and dimethylformamide (50mL) and stir overnight at room temperature under argon atmosphere. Dilute the mixture with ice-water, acidify with aqueous hydrochloric acid and extract
5 with ethyl ether. Wash the ethereal layer with water, then brine, filter through fluorosil- Na_2SO_4 and evaporate to an orange semi-solid (4.0g). Purify the product by first distilling (180-200°C @ 0.1 mm Hg) then subjecting to silica gel chromatography (CCl_4) to obtain the title compound as a
10 colorless oil which slowly crystallizes.

Anal. Calcd for $\text{C}_{29}\text{H}_{54}\text{OSSi}$: C, 72.73; H, 11.37; S, 6.70;
Found: C, 71.26; H, 11.34; S, 6.93.

15

Example 32,6-Di-t-butyl-4[(trimethylsilyl)methyl]thio-phenol

Mix 2,6-di-t-butyl-4-mercaptophenol (2.4g, 10mmol), potassium carbonate (1.4g, 10mmol), and dimethylacetamide
20 (50mL) and stir at room temperature under argon atmosphere. Add chloromethyltrimethylsilane (1.3g, 10mmol) and stir overnight. Warm on a steam bath for 2 hours, cool, and dilute with water. Extract with ethyl ether, dry, evaporate to a light yellow solid (2.8g) and recrystallize (CH_3CN) to give
25 1.1g (34%) of the title compound; mp 100-101°C.

Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{OSSi}$: C, 66.60; H, 9.88; S, 9.88;
Found: C, 66.83; H, 10.05; S, 9.91.

30

Example 42,6-Dimethyl-4[(trimethylsilyl)methoxy]phenol

Mix 2,6-dimethylhydroquinone (1.4g, 10mmol), potassium carbonate (1.4g, 10mmol), chloromethyltrimethylsilane (1.9g,
35 10mmol) and dimethylformamide (50mL). Stir at room

-9-

temperature under inert atmosphere until the reaction is complete. Dilute the mixture with ice-water and extract with ethyl ether. Wash the ethereal layer with water, then brine and filter through fluorosil- Na_2SO_4 . Evaporate to give the
5 title compound and purify by silica gel chromatography.

The following compounds can be prepared by procedures analogous to those described above in Examples 1-4:

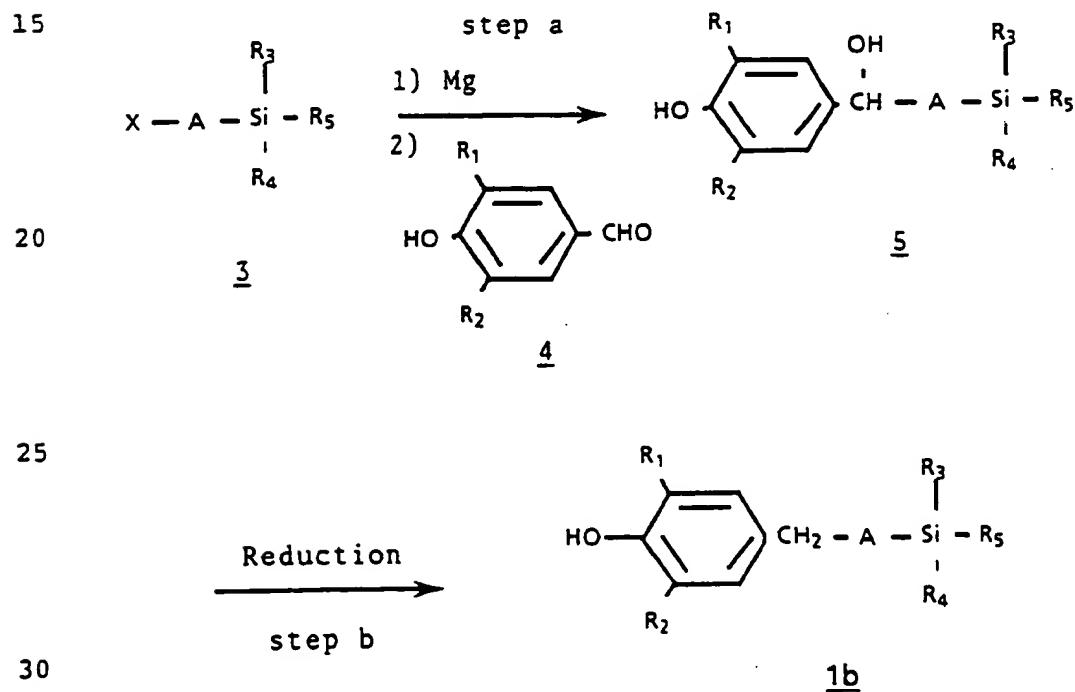
- 2,6-di-t-butyl-4[(triethylsilyl)methyl]thiophenol
- 10 2,6-di-t-butyl-4[(diethylphenylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(tripropylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(dipropylphenylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(triisopropylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(diisopropylphenylsilyl)methyl]thiophenol
- 15 2,6-di-t-butyl-4[(tributylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(dibutylphenylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(triisobutylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(diisobutylphenylsilyl)methyl]thiophenol
- 2,6-di-t-butyl-4[(tri-t-butylsilyl)methyl]thiophenol
- 20 2,6-di-t-butyl-4[(di-t-butylphenylsilyl)methyl]thiophenol
- 2,6-di-methyl-4[(trimethylsilyl)methyl]thiophenol
- 2,6-di-methyl-4[(dimethylphenylsilyl)methyl]thiophenol
- 2,6-di-methyl-4[(dibutylphenylsilyl)methyl]thiophenol
- 2,6-di-methyl-4[(tri-t-butylsilyl)methyl]thiophenol
- 25 2,6-di-methyl-4[(di-t-butylphenylsilyl)methyl]thiophenol
- 2,6-di-ethyl-4[(trimethylsilyl)methyl]thiophenol
- 2,6-di-ethyl-4[(dimethylphenylsilyl)methyl]thiophenol
- 2,6-di-ethyl-4[(tri-t-butylsilyl)methyl]thiophenol
- 2,6-di-ethyl-4[(di-t-butylphenylsilyl)methyl]thiophenol
- 30 2,6-di-propyl-4[(trimethylsilyl)methyl]thiophenol
- 2,6-di-propyl-4[(dimethylphenylsilyl)methyl]thiophenol
- 2,6-di-isopropyl-4[(trimethylsilyl)methyl]thiophenol
- 2,6-di-isopropyl-4[(dimethylphenylsilyl)methyl]thiophenol
- 2,6-di-butyl-4[(trimethylsilyl)methyl]thiophenol
- 35 2,6-di-butyl-4[(dimethylphenylsilyl)methyl]thiophenol

-10-

- 2,6-dimethyl-4[(trimethylsilyl)methoxy]phenol
 2,6-dimethyl-4[(dimethylphenylsilyl)methoxy]phenol
 2,6-dibutyl-4[(triethylsilyl)methoxy]phenol
 2,6-dibutyl-4[(diethylphenylsilyl)methoxy]phenol
 5 2,6-di-t-butyl-4[(trimethylsilyl)methoxy]phenol
 2,6-di-t-butyl-4[(dimethylphenylsilyl)methoxy]phenol.

A general synthetic scheme for preparing compounds of formula 1 wherein Z is methylene is set forth in Scheme B,
 10 wherein all substituents, unless otherwise indicated, are previously defined.

Scheme B



-11-

In general, a phenol of structure 1b can be prepared according to Scheme B in a two-step process. In step a, the appropriate haloalkylenesilane of structure 3 is reacted with magnesium metal in a suitable aprotic solvent, such as ethyl ether, in order to form the magnesium halide salt. The magnesium halide salt (Grignard reagent) is then reacted with the appropriate 3,5-dialkyl-4-hydroxy-benzaldehyde of structure 4 (or a suitably protected derivative) to give the alcohol of structure 5. In step b, the alcohol of structure 5 can be reduced to the desired phenol of structure 1b by a variety of reduction techniques and procedures as are well known and appreciated in the art. For example, the alcohol of structure 5 can be reduced by means of a Birch reduction by reacting it with sodium in liquid ammonia.

15

Starting materials for use in the general synthetic procedures outlined in Scheme B are readily available or can readily be prepared according to standard techniques and procedures. Where necessary to prevent undesired side reactions, the 1-phenol functionality of the 3,5-dialkyl-4-hydroxy-benzaldehyde of structure 4 in Scheme B may be blocked prior to the Grignard reaction with a standard phenol blocking agent as described previously in Scheme A.

25 The following example presents a typical synthesis as described in Scheme B. This example is understood to be illustrative only and is not intended to limit the scope of the present invention in any way.

30

Example 52,6-Dimethyl-4[2-(trimethylsilyl)ethyl]phenol

Step a: Mix magnesium turnings (240mg, 10mmol) and anhydrous ethyl ether under an inert atmosphere. Add a solution of chloromethyltrimethylsilane (1.9g, 10mmol) in anhydrous ethyl

35

-12-

ether. Stir until the magnesium metal dissolves. Add a solution of 3,5-dimethyl-4-hydroxybenzaldehyde (1.5g, 10mmol) in anhydrous ethyl ether. Stir until reaction is complete. Cool the reaction mixture to 0°C and add saturated ammonium chloride solution. Separate the ether layer, wash with water and dry (MgSO₄). Evaporate to give 4-hydroxy-3,5-dimethyl-α-[(trimethylsilyl)-methyl]benzenemethanol and purify by silica gel chromatography.

Step b: Mix sodium metal (520mg, 22.6mmol) and liquid ammonia (13mL). To this solution add, by dropwise addition, a solution of 4-hydroxy-3,5-dimethyl-α-[(trimethylsilyl)-methyl]benzenemethanol (2.22g, 10mmol) in ethyl alcohol (0.5g) and ethyl ether (5ml). After the blue color disappears, cautiously add water (13mL), extract with ethyl ether, dry (MgSO₄), and evaporate the solvent. Purify the residue by silica gel chromatography to yield the title compound.

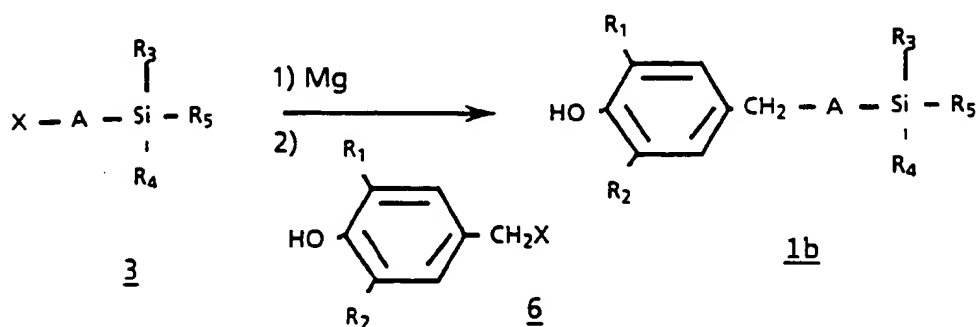
Alternatively, compounds of formula (1) wherein Z is methylene can be prepared according to the procedure set forth in Scheme C, wherein all substituents, unless otherwise indicated, are previously described.

Scheme C

25

30

35



-13-

In general, a phenol of structure 1b can be prepared by first reacting the appropriate haloalkylenesilane of structure 3 with magnesium metal in an suitable aprotic solvent, such as ethyl ether, in order to form the magnesium halide salt. The magnesium halide salt (Grignard Reagent) is then reacted with the appropriate 3,5-dialkyl-4-hydroxy-benzylhalide of structure 6 (or a suitably protected derivative) to give the desired phenol of structure 1b.

10

Starting materials for use in the general synthetic procedures outlined in Scheme C are readily available or can readily be prepared according to standard techniques and procedures. For example, the preparation of 3,5-dimethyl-4-acetoxy-benzylbromide is described in *Tetrahedron* 33, 3097-103 (1977). 3,5-Dimethyl-4-acetoxy-benzylbromide can be converted to the corresponding phenolic starting material by standard hydrolytic procedures.

20 Where necessary to prevent undesired side reactions, the 1-phenol functionality of the 3,5-dialkyl-4-hydroxy-benzylhalide of structure 6 in Scheme C may be blocked prior to the Grignard reaction with a standard phenol blocking agent as described previously in Scheme A.

25

The following example presents a typical syntheses as described in Scheme C. This example is understood to be illustrative only and is not intended to limit the scope of the present invention in any way.

30

Example 6

2,6-diethyl-4-[2-(trimethylsilyl)ethyl]-phenol

Mix magnesium turnings (240mg, 10mmol) and anhydrous ethyl ether under an inert atmosphere. Add a solution of

35

-14-

chloromethyltrimethylsilane (1.9g, 10mmol) in anhydrous ethyl ether. Stir until the magnesium metal dissolves. Add a solution of 4-bromomethyl-2,6-diethylphenol (2.43g, 10mmol) in anhydrous ethyl ether and reflux the mixture until the
5 reaction is complete. Pour onto a mixture of ice/hydrochloric acid and separate the layers. Wash the ethereal layer with water, dry (MgSO₄) and evaporate to give the title compound which is purified by silica gel chromatography.

10 The following compounds can be prepared by procedures analogous to those described above in Examples 5 and 6:

- 2,6-dipropyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 2,6-dipropyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol
- 2,6-diisopropyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 15 2,6-diisopropyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol
- 2,6-diisobutyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 2,6-diisobutyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol
- 2,6-dibutyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 2,6-dibutyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol
- 20 2,6-di-t-butyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 2,6-di-t-butyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol
- 2,6-di-t-butyl-4-[2-(tri-t-butylsilyl)ethyl]-phenol
- 2,6-di-t-butyl-4-[2-(di-t-butylphenylsilyl)ethyl]-phenol
- 2,6-dimethyl-4-[2-(trimethylsilyl)ethyl]-phenol
- 25 2,6-dimethyl-4-[2-(dimethylphenylsilyl)ethyl]-phenol.

It is understood that compounds of formula (1) may exist in various stereoisomeric forms. All stereoisomeric forms which are consistent with the above structural formulas, as
30 interpreted according to standard conventions for expressing stereoisomeric structure, are intended to be included within the scope of the present invention.

Compounds of formula (1), e.g. 2,6-di-alkyl-4-silyl-
35 phenols, are known in the art. Specifically, compounds of

-15-

formula (1) are described in U.S.P. 5,155,250. Preferred compounds of formula (1) are those in which R_1 and R_2 are C_4 alkyl group, R_3 and R_4 are a C_1 alkyl group, A is a C_1 alkylene group, and R_5 is $-(CH_2)_n-(Ar)$ where n is 0 and Ar is phenyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C_1 - C_6 alkyl. More preferred is the compound 2,6-di-t-butyl-4[(dimethylphenylsilyl)methyl]-thio-phenol.

10

As used herein, the term "patient" refers to warm-blooded animals or mammals, including rabbits and humans, who are in need of lowering plasma cholesterol levels or in need of lowering plasma LDL levels.

15

Hypercholesterolemia is a disease state characterized by the excessive cholesterol levels in the blood. The identification of patients with hypercholesterolemia and who are in need of treatment is well within the ability and knowledge of one skilled in the art. For example, individuals who are either suffering from clinically significant hypercholesterolemia or who are at risk of developing clinically significant hypercholesterolemia are patients in need of treatment. A clinician skilled in the art can readily determine, by the use of clinical tests, physical examination and medical/family history, if an individual is a patient in need of treatment for hypercholesterolemia.

An effective amount of a compound of formula (1) is an amount which is effective in inhibiting development or growth of hypercholesterolemia in a patient in need thereof. As such, successful treatment of a patient for hypercholesterolemia is understood to include effectively reducing or lowering serum cholesterol levels in a patient's blood and does not necessarily indicate a total elimination of

-16-

the cholesterol. It is further understood and appreciated by those skilled in the art that successful treatment for hypercholesterolemia includes the use as a prophylactic to prevent clinically significant elevated levels of serum
5 cholesterol.

An effective amount of a compound of formula (1) can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances.
10 In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the
15 particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

20 An effective amount of a compound of formula (1) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 5 grams per kilogram of body weight per day (gm/kg/day). A daily dose of from about 1 mg/kg to about 500 mg/kg is preferred.

25

In effecting treatment of a patient, a compound of formula (1) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the
30 compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration

35

-17-

depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

A compound of formula (1) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining a compound of formula (1) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

10

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

20

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, a compound of formula (1) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of a compound of formula (1), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a unit dosage form suitable for administration will be obtained.

35

-18-

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents
5 such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When
10 the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus,
15 tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should
20 be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, a compound of formula (1) may be incorporated into a solution or suspension. These preparations should contain at least 0.1%
25 of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the active ingredient present in such compositions is such that a suitable dosage will be obtained.

30 The solutions or suspensions may also include one or more of the following adjuvants depending on the solubility and other properties of a compound of formula (1): sterile
diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or
35 other synthetic solvents; antibacterial agents such as benzyl

-19-

alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

The following examples illustrate the use of compounds of formula (1) according to the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

15

Example 7

Reduction of Cholesterol Levels of 1% Cholesterol-Fed New Zealand White Rabbits by Concurrent Administration of 0.5% MDL 29,353

20 New Zealand White (NZW) rabbits (female, aged 3-4 months, weighing less than 3 kg) six in each group, were fed a control diet of 1% cholesterol (100g rabbit chow daily containing 1g cholesterol) or a diet of 1% cholesterol/0.5% drug (100g rabbit chow daily containing 1g cholesterol and 0.5 g MDL 29,353). After 56 days, the rabbits were sacrificed by intravenous injection of pentobarbital. Plasma or serum was collected and cholesterol levels were determined using the enzymatic method of Mao, et al., Clin. Chem. (1983) 29:1890-1897. The results obtained are summarized in Table 1, below:

25

30

35

-20-

Table 1

REDUCTION OF SERUM CHOLESTEROL LEVELS OF 1% CHOLESTEROL-FED
NEW ZEALAND WHITE RABBITS BY CONCURRENT ADMINISTRATION OF 0.5%
MDL 29,353

| | | | |
|----|-----|--------------------------------------|--|
| 5 | Day | Control (n=6) Cholesterol (mg/dl) | MDL 29,353(n=6) Cholesterol (mg/dl) |
| | 0 | 61 ± 9 | 59 ± 8 |
| | 14 | 1138 ± 134 | 684 ± 99 |
| 10 | 28 | 1908 ± 256 | 954 ± 126 |
| | 42 | 2175 ± 376 | 1118 ± 164 |
| | 56 | 2432 ± 475 | 1035 ± 152 |

At day 56, the reduction of serum cholesterol was 57% by the
15 administration of MDL 29,353.

Example 8

Reduction of Cholesterol levels of 0.2% Cholesterol-Fed
New Zealand White Rabbits by Concurrent Administration of
20 0.4% MDL 29,353

NZW rabbits (female, aged 3-4 months, weighing less than 3
Kg), six in each group, were fed a control diet of 0.2%
cholesterol (100 g rabbit chow daily containing 0.2 g
25 cholesterol) or a diet of 0.2% cholesterol/0.4% drug (100 g
rabbit chow daily containing 0.2 g cholesterol and 0.4 g MDL
29,353). After 56 days, the rabbits were sacrificed by
intravenous injection of pentobarbital. Plasma or serum was
collected and cholesterol levels were determined using the
30 enzymatic method of Mao, et al., Clin. Chem. (1983) 29:1890-
1897. The results obtained are summarized in Table 2 below:

-21-

Table 2

| Day | Control (n=6) Cholesterol(mg/dl) | MDL 29,353 (n=6) Cholesterol(mg/dl) |
|-----|-------------------------------------|--|
| 0 | 73 ± 10 | 66 ± 8 |
| 7 | 325 ± 43 | 154 ± 17 |
| 14 | 587 ± 71 | 223 ± 32 |
| 28 | 898 ± 126 | 291 ± 59 |
| 42 | 988 ± 147 | 357 ± 89 |
| 56 | 941 ± 163 | 337 ± 100 |

The results obtained demonstrate that administration of MDL 29,353 for 56 days produced significant cholesterol lowering in 0.2% cholesterol-fed rabbits. The reduction of cholesterol was 64%.

Example 9

Reduction in Cholesterol Levels of Normolipidemic
New Zealand Rabbits by Concurrent Administration of 0.5%
MDL 29,353

New Zealand White rabbits (female, aged 3-4 months, weighing less than 3 kg), four in each group, were fed a normal diet (100 g rabbit chow daily) or a diet of 0.5% drug (100 g rabbit chow daily containing 0.5 g MDL 29,353). Serum was collected and cholesterol levels were determined according to the method of Mao, et al., Clin. Chem. (1983) 29:1890-1897. The results are summarized in Table 3 below:

-22-

Table 3

REDUCTION OF SERUM CHOLESTEROL LEVELS IN NEW ZEALAND
WHITE RABBITS ON NORMAL DIET WITH CONCURRENT ADMINISTRATION
OF 0.5% MDL 29,353.

| | | | |
|----|-----|-------------------------------------|--|
| 5 | Day | Control (n=4) Cholesterol(mg/dl) | MDL 29,353 (n=4) Cholesterol(mg/dl) |
| | 0 | 47.0 ± 11 | 45.3 ± 4 |
| | 8 | 90.0 ± 13 | 69.7 ± 6 |
| 10 | 14 | 87.3 ± 7 | 54.8 ± 8 |
| | 23 | 81.5 ± 68 | 58.3 ± 6 |

As compared to control rabbits at day 23, the level of
cholesterol was significantly reduced by about 29%.

15

20

25

30

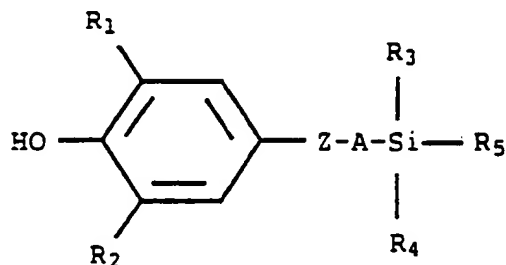
35

-23-

WHAT IS CLAIMED IS:

1. A method for lowering plasma cholesterol level in a patient by administration of a compound of formula (1)

5



15

wherein:

R₁, R₂, R₃ and R₄ are each independently a C₁-C₆ alkyl group;
Z is a thio, oxy or methylene group;

20

A is a C₁-C₄ alkylene group; and

R₅ is a C₁-C₆ alkyl or -(CH₂)_n-(Ar)

wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or naphthyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl group.

25

2. The method according to claim 1, wherein R₁ and R₂ are C₄ alkyl group.

30

3. The method according to claim 1, wherein R₃ and R₄ are C₁ alkyl group.

4. The method according to claim 1, wherein A is a C₁ alkylene group.

35

-24-

5. The method according to claim 1, wherein Z is thio.

6. The method according to claim 1, wherein R₅ is
5 -(CH₂)_n-(Ar) where n is 0 and Ar is phenyl unsubstituted or
substituted with one to three substituents selected from the
group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro
or C₁-C₆ alkyl group.

10 7. The method according to claim 1, wherein R₁ and R₂ are
C₄ alkyl group, R₃ and R₄ are C₁ alkyl group, A is C₁ alkylene
group, and R₅ is -(CH₂)_n-(Ar) where n is 0 and Ar is phenyl
unsubstituted or substituted with one to three substituents
selected from the group consisting of hydroxy, methoxy, ethoxy,
15 chloro, fluoro or C₁-C₆ alkyl group.

8. A method according to the method of claim 1, wherein
the compound is 2,6-di-t-butyl-4[(dimethylphenylsilyl)methyl]-
thio-phenol.

20

25

30

35

AMENDED CLAIMS

[received by the International Bureau on 16 May 1995 (16.05.95);
new claims 9-28 added; remaining claims unchanged (4 pages)]

5. The method according to claim 1, wherein Z is thio.
6. The method according to claim 1, wherein R₅ is
5 -(CH₂)_n-(Ar) where n is 0 and Ar is phenyl unsubstituted or
substituted with one to three substituents selected from the
group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro
or C₁-C₆ alkyl group.
- 10 7. The method according to claim 1, wherein R₁ and R₂ are
C₄ alkyl group, R₃ and R₄ are C₁ alkyl group, A is C₁ alkylene
group, and R₅ is -(CH₂)_n-(Ar) where n is 0 and Ar is phenyl
unsubstituted or substituted with one to three substituents
selected from the group consisting of hydroxy, methoxy, ethoxy,
15 chloro, fluoro or C₁-C₆ alkyl group.
8. A method according to the method of claim 1, wherein
the compound is 2,6-di-t-butyl-4[(dimethylphenylsilyl)methyl]-
thio-phenol.
- 20 9. The method according to claim 1, wherein the patient
is suffering from restenosis, angina, cerebral
arteriosclerosis, or xanthoma.
- 25 10. The method according to claim 9, wherein the patient
is suffering from restenosis.
11. The method according to claim 9, wherein the patient
is suffering from agina.
- 30 12. The method according to claim 9, wherein the patient
is suffering from cerebral arteriosclerosis.
13. The method according to claim 9, wherein the patient
35 is suffering from xanthoma.

14. The method according to claim 1, wherein the patient is at risk of developing restenosis, angina, cerebral arteriosclerosis, or xanthoma.

15. The method according to claim 14, wherein the patient is suffering from restenosis.

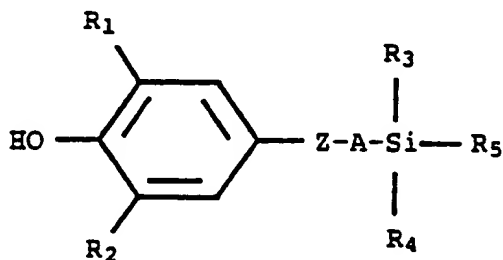
16. The method according to claim 14, wherein the patient is suffering from angina.

17. The method according to claim 14, wherein the patient is suffering from cerebral arteriosclerosis.

18. The method according to claim 14, wherein the patient is suffering from xanthoma.

19. The use of a compound of formula (1)

wherein:



R₁, R₂, R₃ and R₄ are each independently a C₁-C₆ alkyl group;

Z is a thio, oxy or methylene group;

A is a C₁-C₄ alkylene group; and

R₅ is a C₁-C₆ alkyl or -(CH₂)_n-(Ar)

wherein n is an integer 0, 1, 2 or 3; and Ar is phenyl or naphthyl unsubstituted or substituted with

one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl group, C₁-C₆ alkyl group, in the manufacture of a medicament for lowering the plasma cholesterol level in a patient in need thereof.

20. The use of a compound according to claim 19, wherein R₁ and R₂ are C₄ alkyl group.

21. The use of a compound according to claim 19, wherein R₃ and R₄ are C₁ alkyl group.

22. The use of a compound according to claim 19, wherein A is a C₁ alkylene group.

23. The use of a compound according to claim 19, wherein Z is thio.

24. The use of a compound according to claim 19, wherein R₅ is (CH₂)_n-(Ar) where n is 0 and Ar is phenyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl group.

25. The use of a compound according to claim 19, wherein R₁ and R₂ are C₄ alkyl group, R₃ and R₄ are C₁ alkyl group, A is C₁ alkylene group, and R₅ is -(CH₂)_n-(Ar) where n is 0 and Ar is phenyl unsubstituted or substituted with one to three substituents selected from the group consisting of hydroxy, methoxy, ethoxy, chloro, fluoro or C₁-C₆ alkyl group.

26. The use of a compound according to claim 19, wherein the compound is 2,6-di-t-butyl-4[(dimethylphenylsilyl)methyl]-thio-phenol.

27. The use of a compound according to claim 19, wherein the patient is suffering from restenosis, angina, cerebral arteriosclerosis or xanthoma.

28. The use of a compound according to claim 19, wherein the patient is at risk of developing restenosis, angina, cerebral arteriosclerosis, or xanthoma.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/12702

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/695

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | EP,A,0 464 852 (MERRELL DOW) 8 January 1992 cited in the application see the whole document & US,A,5 155 250 (PARKER ET AL.) --- | 1-8 |
| Y | EP,A,0 464 844 (MERRELL DOW) 8 January 1992 see the whole document --- | 1-8 |
| Y | EP,A,0 372 542 (MERRELL DOW) 13 June 1990 see the whole document --- -/-- | 1-8 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

1 March 1995

Date of mailing of the international search report

1 7. 03. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/US 94/12702

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | PROC. NATL. ACAD. SCI., vol. 84, no.21, 1987 pages 7725-7729, T.E. CAREW ET AL. 'ANTIATHEROGENIC EFFECT OF PROBUCOL UNRELATED TO ITS HYPOCHOLESTEROLEMIC EFFECT' see the whole document ----- | 1-8 |
| A | FR,A,2 308 372 (SOCIETE CIVILE D'ETUDE DE PHARMACOLOGIE APPLIQUEE) 19 November 1976 see the whole document ----- | 1-8 |
| A | US,A,4 670 421 (DEVRIES ET AL.) 2 June 1987 see the whole document ----- | 1-8 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 94/12702

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP-A-464852 | 08-01-92 | US-A- 5155250 | 13-10-92 |
| | | AU-B- 639576 | 29-07-93 |
| | | AU-A- 8011691 | 09-01-92 |
| | | CA-A- 2046051 | 06-01-92 |
| | | CN-A- 1057843 | 15-01-92 |
| | | JP-A- 4230393 | 19-08-92 |
| | | NZ-A- 238808 | 25-02-94 |
| EP-A-464844 | 08-01-92 | AU-B- 639807 | 05-08-93 |
| | | AU-A- 8011491 | 09-01-92 |
| | | CA-A- 2046050 | 06-01-92 |
| | | CN-A- 1057842 | 15-01-92 |
| | | JP-A- 4230394 | 19-08-92 |
| | | NZ-A- 238807 | 25-03-94 |
| | | US-A- 5304668 | 19-04-94 |
| | | US-A- 5281738 | 25-01-94 |
| EP-A-372542 | 13-06-90 | US-A- 4900757 | 13-02-90 |
| | | AU-B- 619926 | 06-02-92 |
| | | AU-A- 4588489 | 14-06-90 |
| | | ES-T- 2052871 | 16-07-94 |
| | | JP-A- 2202817 | 10-08-90 |
| | | US-A- 4954528 | 04-09-90 |
| FR-A-2308372 | 19-11-76 | DE-A- 2538292 | 18-03-76 |
| | | GB-A- 1508338 | 19-04-78 |
| | | JP-A- 52015829 | 05-02-77 |
| | | JP-A- 52038034 | 24-03-77 |
| | | LU-A- 73351 | 13-04-76 |
| | | NL-A- 7510317 | 12-03-76 |
| | | OA-A- 5105 | 31-01-81 |
| | | US-A- 4000265 | 28-12-76 |
| US-A-4670421 | 02-06-87 | NONE | |